Prostate Cancer

PCA3 Urinary Biomarker for Prostate Cancer

Reviewed by Stacy Loeb MD, Alan W. Partin MD, PhD
The James Buchanan Brady Urological Institute, Department of Urology, Johns Hopkins Medical Institutions, Baltimore, MD

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A major ongoing problem in prostate cancer screening is the limited specificity of prostate-specific antigen (PSA) testing. Elevations in serum PSA levels may occur in numerous benign conditions, leading to unnecessary biopsies. Moreover, PSA levels reflect the spectrum of prostate cancer (PCa) risk, such that a proportion of PCas will be missed using the traditional PSA thresholds.[1]

These issues have paved the way for widespread investigation into alternate PCa biomarkers. In 1999, Bussemakers and colleagues found that the DD3(PCA3) gene was highly overexpressed in PCa tissue compared with adjacent benign prostatic hyperplasia (BPH) or normal prostate tissue.[2] They also reported no detectable DD3 expression in numerous nonprostatic normal tissues and tumors (bladder, breast, cervix, endometrium, kidney, ovary, and testis), suggesting that DD3 was prostate specific. These discoveries led to the hypothesis that PCA3 may be useful as a marker for PCa diagnosis.[3]

Since that time, a quantitative urinary assay for PCA3 messenger RNA (mRNA) has been developed and several studies have examined the role of PCA3 in screening. This article reviews contemporary studies on PCA3 performance in men undergoing prostate biopsy.

PCA3 Molecular Urine Assay for Prostate Cancer in Men Undergoing Repeat Biopsy

Marks LS, Fradet Y, Deras IL, et al.

J Urol. 2007;69:532-535.

This was among the first clinical studies to evaluate the role of PCA3 in PCa screening and detection in 233 men with a PSA level ≥ 2.5 ng/mL and at least 1 prior negative prostate biopsy. PCA3 scores were calculated as the ratio of urinary PCA3 mRNA to PSA mRNA ×1000, as a means to correct for the amount of prostate RNA present in the specimen.

A total of 226 (97%) specimens yielded sufficient RNA for a PCA3 calculation, and 60 (26.5%) of these men were diagnosed with PCa. On receiver operating characteristic (ROC) analysis, PSA had an area under the curve (AUC) of 0.524, whereas PCA3 had an AUC of 0.678 for PCa detection on repeat biopsy. A PCA3 threshold of 35 was associated with 58% sensitivity and 72% specificity.

Overall, PCA3 scores had a significant direct relationship with the probability of PCa on repeat biopsy. For example, only 12% of men with a PCA3 score < 5 had a positive biopsy, compared with 50% of those with PCA3 scores > 100. The authors concluded that PCA3 may be useful for risk stratification in men with a prior negative prostate biopsy.

These results have since been confirmed in separate populations of men undergoing both initial and repeat prostate biopsy.[4,5] Furthermore, nomograms have been developed that incorporate PCA3 along with other clinical variables to predict prostate biopsy results.[6]

Performance of the PCA3 Gene and PSA in Prescreened Men: Exploring the Value of PCA3 for a First-Line Diagnostic Test

Roobol MJ, Schroder FH, van Leeuwen P, et al.

Eur Urol. 2010;58:475-481.

In a more recent study, Roobol and colleagues prospectively evaluated PCA3 in previously screened men from the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. The analysis included 721 men who underwent sextant biopsy for a PSA ≥ 3 ng/mL alone (n = 32), PCA3 score ≥ 10 alone (n = 492), or both indications (n = 197).

In total, 122 (16.9%) PCas were diagnosed. A PSA cutoff of 3 ng/mL had 35.2% sensitivity and 69.0% specificity in this prescreened population. By contrast, a PCA3 score ≥ 10 had 69.7% sensitivity and 4.7% specificity for PCa detection. Instead, using a PCA3 threshold of 35, sensitivity was 68.0%, with a specificity of 55.7%.

Of the PCas diagnosed in this study, 19 (15.6%) were classified as "serious" based on a clinical stage > T2a and/or Gleason pattern ≥ 4. Using a PSA cutoff of 3 ng/mL would have missed 79 of 122 (64.7%) cancers, of which 11 were "serious" cancers. PCA3 cutoffs of 10 and 35 would have missed 4 (3.3%) and 39 (32%) cancers, respectively, including 0 and 5 which met the criteria for "serious" tumors. However, 492 (68.3%), 32 (4.4%), and

373 (51.7%) biopsies would have been spared using a PSA threshold of 3 ng/mL, PCA3 cutoff of 10, and PCA3 cutoff of 35 in this population, respectively.

On ROC analysis, PSA had an AUC of 0.581 for PCa detection, as compared with 0.635 for PCA3. In the subset with prior negative biopsy, PCA3 had a higher AUC of 0.681. Finally, at PSA levels < 3 ng/mL, the AUC of PCA3 for PCa detection was 0.627.

Although these numbers suggest that PCA3 improves discrimination beyond PSA, it must be noted that these men had already undergone multiple rounds of PSA screening. Accordingly, much of the predictive power of PSA may have already been expended during earlier screening rounds.

That notwithstanding, these combined findings suggest a potential role for PCA3 in men with prior PSA screening and/or prostate biopsy to aid in risk stratification. The relationship of PCA3 to PCa aggressiveness and its role in prognostication require further study. ■

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